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on behalf of the International Database on Home blood pressure in relation to Cardiovascular Outcome (IDHOCO) Investigators

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See Editorial Commentary, pp 670–671

Abstract—Home blood pressure monitoring is useful in detecting white-coat and masked hypertension and is recommended for patients with suspected or treated hypertension. The prognostic significance of white-coat and masked hypertension detected by home measurement was investigated in 6458 participants from 5 populations enrolled in the International Database of HOme blood pressure in relation to Cardiovascular Outcomes. During a median follow-up of 8.3 years, 714 fatal plus nonfatal cardiovascular events occurred. Among untreated subjects ($n=5007$), cardiovascular risk was higher in those with white-coat hypertension (adjusted hazard ratio 1.42; 95% CI [1.06–1.91]; $P=0.02$), masked hypertension (1.55; 95% CI [1.12–2.14]; $P<0.01$) and sustained hypertension (2.13; 95% CI [1.66–2.73]; $P<0.0001$) compared with normotensive subjects. Among treated patients ($n=1451$), the cardiovascular risk did not differ between those with high office and low home blood pressure (white-coat) and treated controlled subjects (low office and home blood pressure; 1.16; 95% CI [0.79–1.72]; $P=0.45$). However, treated subjects with masked hypertension (low office and high home blood pressure; 1.76; 95% CI [1.23–2.53]; $P=0.002$) and uncontrolled hypertension (high office and home blood pressure; 1.40; 95% CI [1.02–1.94]; $P=0.04$) had higher cardiovascular risk than treated controlled patients. In conclusion, white-coat hypertension assessed by home measurements is a cardiovascular risk factor in untreated but not in treated subjects probably because the latter receive effective treatment on the basis of their elevated office blood pressure. In contrast, masked uncontrolled hypertension is associated with increased cardiovascular risk in both untreated and treated patients, who are probably undertreated because of their low office blood pressure. (*Hypertension*. 2014;63:675–682.) • [Online Data Supplement](#)

Key Words: cardiovascular diseases ■ home blood pressure monitoring ■ masked hypertension
■ meta-analysis ■ prognosis ■ white-coat hypertension

Conventional measurement of blood pressure (BP) at the doctor's office is considered as the standard method for hypertension diagnosis and management.¹ However, white-coat and masked hypertension phenomena are common in both untreated and treated patients. Assessment of out-of-office BP

with ambulatory or home monitoring is therefore necessary for an accurate diagnosis and management.¹

According to the European Society of Hypertension recommendations, white-coat and masked hypertension can be diagnosed using ambulatory or home BP measurements, with

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From the Hypertension Center, Third University Department of Medicine, Sotiria Hospital, Athens, Greece (G.S.S., A. K.); Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Belgium (K.A., L.T., J.A.S.); Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan (K.A., T.O., Y.I.); Population Studies Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Turku, Finland (T.J.N., J.K.J., A.M.J.); Department of Medicine, Turku University Hospital, Finland (T.J.N.); Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan (A.H.); Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay (J.B.); Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan (T.O.); Department of Public Health, Tohoku University Graduate School of Medicine, Sendai, Japan (I.T.); and Department of Epidemiology, Maastricht University, The Netherlands (J.A.S.).

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Correspondence to Jan A. Staessen, Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Block D, Box 7001, BE-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be or jan.staessen@epid.unimaas.nl

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white-coat hypertension defined as elevated office and low ambulatory or home BP, and masked hypertension the reverse.¹ However, the European recommendations state that ambulatory and home BP monitoring might not be fully interchangeable methods.¹ The role of ambulatory BP monitoring in predicting cardiovascular events has been well established,¹ whereas for home BP monitoring until recently there was only 1 outcome study.² In the past years, more prognostic data for home BP became available.^{3–5} Home BP monitoring is being widely used in several countries, and current guidelines in Europe and the US recommend its use in all treated patients with hypertension and in untreated subjects with suspected hypertension.^{6,7}

The International Database of Home blood pressure in relation to Cardiovascular Outcome (IDHOCO) has been constructed using individual participants' data of published population studies that evaluated the prognostic value of home BP.^{8,9} The collective analysis of the available outcome studies provided adequate power to allow the investigation of the prognostic significance of white-coat and masked hypertension phenomena separately in untreated and treated subjects, which was the objective of this article.

Methods

Study Population

The IDHOCO database⁸ has been constructed using individual subjects' data including information on subsequent fatal and nonfatal outcomes obtained from 5 population studies of home BP monitoring performed in Ohasama, Japan (n=2777),^{10,11} Finland (Finn-Home; n=2075),³ Tsurugaya, Japan (n=836),¹² Didima, Greece (n=665),¹³ and Montevideo (n=400).¹⁴ The classification and number of events, and baseline characteristics have been published.^{8,9} Of a total of 6753 participants in the IDHOCO database, 295 participants were excluded (284 with <2 office or home BP readings; 10 with missing information for baseline treatment; 1 without information on cardiovascular disease history).⁸

Office and Home BP Measurements

At least 2 baseline office and home BP measurements were required for inclusion. Office measurements were taken using electronic (3 studies)^{10,12,14} or mercury manometers (2 studies),^{3,13} in a single visit (4 studies)^{3,10,12,14} or 2 visits (1 study),¹³ and the average number of BP readings per study ranged from 1.8 to 6.⁸ Home measurements were taken using validated electronic arm devices in the morning and evening (4 studies),^{3,10,13,14} or only the morning (1 study),¹² and the total number of BP readings averaged per study ranged from 2 to 45.9 (4 studies including 94% of the participants provided an average of ≥ 12 readings).^{3,10,12,13} Home monitoring was performed only at baseline within 1 to 26 days (≥ 7 days in 84% of the participants).^{3,10,12} Office BP measurements of a single visit and all available home measurements of each individual were averaged to give a single number for office and home BP, respectively.

Definitions of White-coat, Masked, and Sustained Hypertension

White-coat hypertension was defined as office systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, with home systolic BP < 135 mmHg and diastolic BP < 85 mmHg. Masked hypertension was defined as home systolic BP ≥ 135 mmHg and/or diastolic BP ≥ 85 mmHg, with office systolic BP < 140 mmHg and diastolic BP < 90 mmHg. Sustained hypertension was defined as elevated office BP (systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg) and home (systolic BP ≥ 135 mmHg and/or diastolic BP ≥ 85 mmHg) and normotension as low office (systolic BP < 140 mmHg and diastolic BP < 90 mmHg) and home (systolic BP < 135 mmHg and diastolic BP < 85 mmHg).

End Points

The primary analysis was based on a composite cardiovascular end point, which included fatal cardiovascular events, nonfatal myocardial infarction, surgical and percutaneous coronary revascularization, heart failure, pacemaker implantation, and stroke. Only the first cardiovascular event for each participant during the study follow-up was accepted for analysis. A secondary analysis including only fatal events (cardiovascular and other) was also performed.

Analysis

The statistical software SAS version 9.3 (SAS Institute, Cary, NC) was used. Means and proportions were compared using the standard normal z test for large samples or ANOVA and the χ^2 statistic, respectively. Kruskal–Wallis test was used to assess differences among subjects with normotension, white-coat, masked, and sustained hypertension. Kaplan–Meier survival curves for cardiovascular events and total mortality were provided in the 4 subgroups, untreated and treated, with ad hoc comparisons (P values with Sidak correction) of normotensives versus subjects with white-coat, masked, and sustained hypertension.

In multivariable-adjusted Cox regression, the hazard ratio for cardiovascular events in subjects with white-coat, masked, and sustained hypertension compared with normotensive subjects was evaluated. Untreated and treated subjects were analyzed separately. Covariables were cohort, sex, age, body mass index, serum cholesterol, smoking, history of cardiovascular disease, and diabetes mellitus. Sensitivity analysis was performed by excluding 1 cohort at a time to confirm that the results are consistent across all studies and not driven by a single cohort.

Results

A total of 6458 subjects were included, with 59239 person-years of follow-up (median 8.3 years; 5th to 95th percentile interval, 4.2–16.8 years). At baseline, 5007 subjects were not on antihypertensive drug treatment (77.5%), whereas 1451 (22.5%) subjects were treated. A total of 714 cardiovascular events occurred during the follow-up (412 in untreated and 302 in treated subjects) and 809 deaths (520 and 289, respectively).

The baseline characteristics of the study participants according to treatment status and the classification into normotensive and white-coat, masked, and sustained hypertension are presented in Table 1. Subjects with masked hypertension were older, had higher incidence of smoking and diabetes mellitus, and tended to have cardiovascular disease history more often than normotensives or subjects with white-coat hypertension (untreated and treated). In white-coat and masked hypertension subjects, both untreated and treated, body mass index, total cholesterol, and office and home BP were higher than in normotensives but lower than in subjects with sustained hypertension. Treated subjects (n=1451) were older (66.6 versus 57.1 years), more likely to have diabetes mellitus (15.6% versus 6.4%) and cardiovascular disease history (23.1% versus 6.5%), less likely to smoke (14.2% versus 22.9%), and had higher body mass index (26.2 versus 25.1 kg/m²) and BP (office 144.4/82.7 versus 130.9/77.9 mmHg; home 138.6/80.3 versus 123.9/74.9 mmHg) than untreated subjects (n=5007; all $P < 0.0001$).

Among subjects with low office BP (normotension and masked hypertension), the proportion of those with elevated home BP (masked hypertension) was higher in treated than in untreated subjects (41.4% versus 11.9%; $P < 0.0001$). On the contrary, among subjects with elevated office BP (sustained plus white-coat hypertension), the proportion of those with low home BP (white-coat hypertension) was higher in untreated than in treated subjects (42.9% versus 25.8%; $P < 0.0001$).

Table 1. Baseline Characteristics in Untreated and Treated Subjects With Normotension and White-Coat, Masked, and Sustained Hypertension

| Characteristics | Untreated Participants | | | | Treated Participants | | | |
|---------------------------|------------------------|---------------|-------------|--------------|----------------------|---------------|-------------|--------------|
| | Normotension | White-Coat HT | Masked HT | Sustained HT | Normotension | White-Coat HT | Masked HT | Sustained HT |
| Subjects, n | 2984 | 695 | 404 | 924 | 328 | 230 | 232 | 661 |
| Age, y | 53.7±13.6 | 58.8±12.1* | 62.7±11.6* | 64.3±11.5* | 65.5±10.4 | 64.3±10.6 | 67.7±9.6† | 67.6±9.7† |
| Sex, women | 1830 (61.3) | 371 (53.4)† | 179 (44.3)* | 458 (49.6)* | 214 (65.2) | 137 (59.6) | 112 (48.3)* | 374 (56.6)† |
| Ethnicity, white | 1482 (49.7) | 324 (46.6) | 184 (45.5) | 531 (57.5)* | 107 (32.6) | 102 (44.4)† | 79 (34.1) | 318 (48.1)* |
| BMI, kg/m ² | 24.3±3.6 | 25.1±3.8* | 26.2±4.6* | 26.8±4.6* | 24.9±3.9 | 25.8±4.3‡ | 26.1±5.2† | 27.0±4.8* |
| Current smoking | 692 (23.2) | 140 (20.1) | 120 (29.7)† | 193 (20.9) | 35 (10.7) | 25 (10.9) | 50 (21.6)§ | 94 (14.4) |
| Total cholesterol, mmol/L | 5.3±1.0 | 5.5±1.1* | 5.4±1.1‡ | 5.8±1.2* | 5.3±1.1 | 5.5±0.9‡ | 5.3±1.0 | 5.7±1.1* |
| Diabetes mellitus | 152 (5.1) | 43 (6.2) | 47 (11.6)* | 76 (8.2)§ | 39 (11.9) | 31 (13.5) | 48 (20.7)† | 108 (16.3) |
| Cardiovascular disease | 155 (5.2) | 48 (6.9) | 37 (9.2)† | 87 (9.4)* | 82 (25.0) | 52 (22.6) | 64 (27.6) | 137 (20.7) |
| Systolic office BP | 119.4±11.7 | 147.8±11.2* | 128.3±8.1* | 156.2±16.0* | 125.2±9.5 | 149.8±12.9* | 128.6±8.7† | 157.5±16.0* |
| Systolic home BP | 114.2±10.1 | 123.6±8.0* | 140.3±9.3* | 148.3±13.1* | 121.8±8.5 | 124.5±7.4† | 143.5±10.6* | 150.2±13.8* |
| Diastolic office BP | 72.6±8.5 | 86.0±9.4* | 76.7±8.3* | 89.9±10.3* | 73.9±8.1 | 85.3±11.1* | 75.7±8.8‡ | 88.6±10.6* |
| Diastolic home BP | 70.2±7.1 | 75.1±6.3* | 84.0±7.4* | 85.9±8.7* | 72.7±6.8 | 75.1±6.3§ | 83.3±7.7* | 84.8±9.3* |

Mean±SD, % in parentheses. BMI indicates body mass index; BP, blood pressure, mm Hg; and HT, hypertension.

* $P<0.0001$.

† $P<0.01$.

‡ $P<0.05$.

§ $P<0.001$ for difference versus normotensives; ANOVA or χ^2 test for comparison among the 4 subgroups (untreated or treated separately) significant for all characteristics ($P<0.05$), apart from cardiovascular disease in treated subjects.

Hazard ratios for cardiovascular events in untreated and treated subjects with white-coat, masked, and sustained hypertension are presented in Table 2 and Kaplan–Meier survival curves in the Figure. Treated normotensive subjects had 54% higher cardiovascular risk than untreated normotensives.

In the untreated group, normotensive subjects had lower cardiovascular risk than subjects with white-coat, masked, and sustained hypertension. The hazard ratio was progressively increased, from normotensives to subjects with white-coat (1.42), masked (1.55), and sustained hypertension (2.13), but with considerable overlap in their 95% confidence intervals (CI; $P<0.0001$ for trend). In the treated group, the hazard ratio of subjects with white-coat hypertension did not differ from treated normotensive patients. As in the untreated group, treated subjects with masked or sustained

hypertension had higher risk than treated subjects with low office and home BP ($P\leq 0.039$).

The hazard ratios for total mortality in untreated and treated subjects with white-coat, masked, and sustained hypertension are presented in Table 3 and Kaplan–Meier survival curves in the Figure. All-cause mortality rates were similar in treated and untreated subjects with normal office and home BP (hazard ratio, 1.10). Subjects with white-coat hypertension, untreated and treated, did not have higher mortality risk than the respective normotensive group (hazard ratio, 1.13 and 1.19, respectively; $P=0.37$). On the contrary, subjects with masked hypertension had higher risk than normotensive subjects, both untreated and treated ($P\leq 0.031$). Untreated subjects with sustained hypertension had higher risk than normotensive subjects ($P=0.012$).

Table 2. Hazard Ratios for Cardiovascular Events in Untreated and Treated Subjects With White-Coat, Masked, and Sustained Hypertension

| Subgroup | Untreated Participants | | | | Treated Participants | | | |
|---------------|------------------------|----------|----------------------|---------|----------------------|----------|----------------------|---------|
| | Subjects N | Events n | Adjusted HR (95% CI) | P Value | Subjects N | Events n | Adjusted HR (95% CI) | P Value |
| Normotensives | 2984 | 154 | 1.00 | | 328 | 57 | 1.54 (1.11–2.14) | 0.01 |
| | | | | | 328 | 57 | 1.00 | |
| White-coat HT | 695 | 64 | 1.42 (1.06–1.91) | 0.019 | 230 | 45 | 1.16 (0.79–1.72) | 0.45 |
| Masked HT | 404 | 53 | 1.55 (1.12–2.14) | 0.008 | 232 | 66 | 1.76 (1.23–2.53) | 0.002 |
| Sustained HT | 924 | 141 | 2.13 (1.66–2.73) | <0.0001 | 661 | 134 | 1.40 (1.02–1.93) | 0.039 |
| Total | 5007 | 412 | | | 1451 | 302 | | |

In the untreated group, hazard ratios express the risk versus untreated normotensives. In the treated group, the hazard ratio of treated normotensives express the risk versus untreated normotensives, whereas the hazard ratios of treated white-coat, masked, and sustained hypertensives express the risk versus treated normotensives. Hazard ratios were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking status, cardiovascular disease history, and diabetes mellitus. CI indicates confidence intervals; HR, hazard ratio; and HT, hypertension.

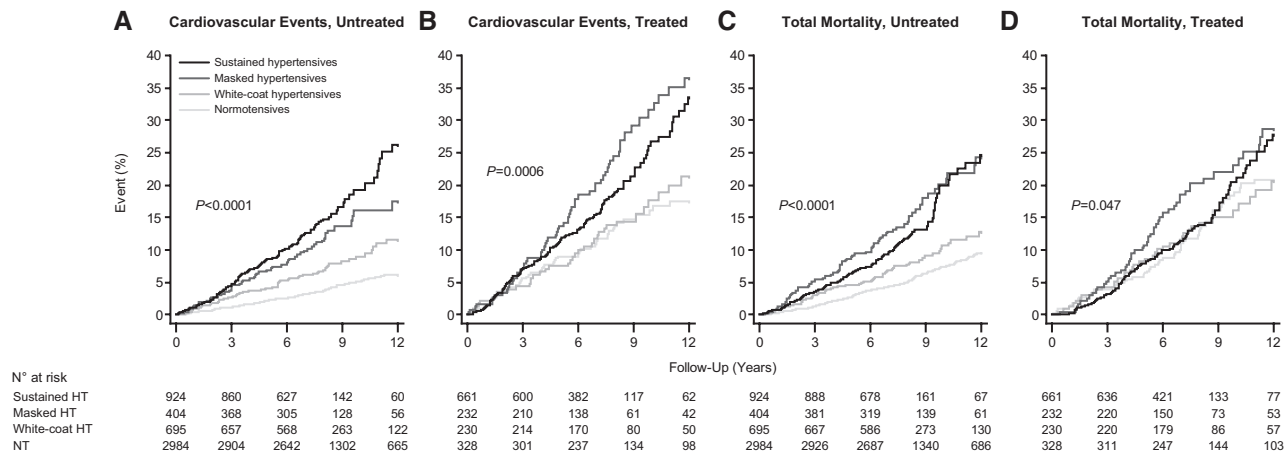


Figure. Kaplan-Meier survival curves for cardiovascular events (A and B) and for total mortality (C and D) in untreated (A and C) and treated subjects (B and D). Lines present normotensives, and subjects with white-coat, masked, and sustained hypertension. *P* values for significance of log-rank test across the 4 categories. Comparison of normotensives versus subjects with white-coat, masked, and sustained hypertension, respectively. A, all $P<0.0001$; (B) 0.49, <0.001 , and 0.03; (C) all <0.0001 ; (D) 0.53, 0.02, and 0.45.

Sensitivity analyses in untreated subjects showed that the cardiovascular risk was 69% (95% CI [17%, 145%]; $P=0.0055$) higher in men with white-coat hypertension compared with normotensive men, whereas the risk in women with white-coat hypertension was similar to that in normotensive women (hazard ratio, 1.13; 95% CI [−32%, 87%]; $P=0.63$). Similarly, men with masked hypertension had 69% (95% CI [13%, 155%]; $P=0.011$) higher cardiovascular risk than normotensive men, whereas the risk in women with masked hypertension was similar to that in normotensive women (hazard ratio, 1.28; 95% CI [0.75, 2.20]; $P=0.37$). Hazard ratios were not significantly different between men and women. Further sensitivity analyses performed by excluding 1 cohort at a time revealed a consistent trend (hazard ratios always to the same direction) toward increased cardiovascular risk in untreated subjects with white-coat, masked, and sustained hypertension compared with untreated normotensive subjects, and in treated, masked, and sustained hypertension compared with treated normalized hypertension (Table S1 in the online-only Data Supplement).

Discussion

The IDHOCO project is unique in that it provides a worldwide, integrated, general population-based, participant level database with data on the prognostic value of home BP measurements. In contrast to each of the individual outcome studies, the IDHOCO database provided the adequate power to allow the investigation of the prognostic significance of white-coat and masked hypertension separately in untreated and treated subjects. Moreover, this type of meta-analysis is superior to literature-based, summary statistics-based meta-analyses because it provides the ability to include the computing survival curves, to check whether the proportional hazard assumption is fulfilled, and test several interactions.^{15,16}

This analysis of home measurements confirms previous reports using ambulatory BP monitoring that masked hypertension is associated with increased cardiovascular risk in both untreated and treated subjects (Table S2).^{17,18} Thus, masked hypertension is a risk factor irrespective of the treatment status and the measurement method (home or ambulatory). However, the novel information provided by this analysis is that the

Table 3. Hazard Ratios for Total Mortality in Untreated and Treated Subjects With White-Coat, Masked, and Sustained Hypertension

| Subgroup | Untreated Participants | | | | Treated Participants | | | |
|---------------|------------------------|-------------|-------------------------|-------------------|----------------------|-------------|-------------------------|-------------------|
| | Subjects N | Events n | Adjusted HR (95% CI) | <i>P</i> Value | Subjects N | Events n | Adjusted HR (95% CI) | <i>P</i> Value |
| Normotensives | 2984 | 239 | 1.00 | | 328 | 62 | 1.10 (0.81–1.48) | 0.55 |
| | | | | | 328 | 62 | 1.00 | |
| White-coat HT | 695 | 75 | 1.13 (0.87–1.46) | 0.37 | 230 | 50 | 1.19 (0.82–1.73) | 0.37 |
| Masked HT | 404 | 76 | 1.36 (1.04–1.77) | 0.024 | 232 | 60 | 1.49 (1.04–2.14) | 0.031 |
| Sustained HT | 924 | 130 | 1.34 (1.07–1.68) | 0.012 | 661 | 117 | 1.19 (0.87–1.64) | 0.28 |
| Total | 5007 | 520 | | | 1451 | 289 | | |

In the untreated group, hazard ratios express the risk versus the untreated normotensives. In the treated group, the hazard ratio of treated normotensives express the risk versus the untreated normotensives, whereas the hazard ratios of treated white-coat, masked, and sustained hypertensives express the risk versus the treated normotensives. Hazard ratios were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking status, cardiovascular disease history, and diabetes mellitus. CI indicates confidence intervals; HR, hazard ratio; and HT, hypertension.

risk associated with white-coat hypertension is increased in untreated but not in treated subjects. The International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) database, which included ambulatory instead of home BP data, did not show a difference in the prognosis of white-coat or masked hypertension in treated versus untreated subjects (Table S2).^{17,18} Thus, these data suggest that in untreated subjects the prognostic relevance of white-coat hypertension might differ according to the method used for out-of-office BP evaluation (home versus ambulatory monitoring), although it should be mentioned that the IDACO and IDHOCO databases differ in more aspects than only the out-of-office BP monitoring method.

Prevalence of White-Coat and Masked Hypertension

In the present study, white-coat hypertension was detected in 14.3% of the participants and, masked hypertension was detected in 9.8% of the participants, compared with 10.6% and 14.6%, respectively, in the IDACO database that also used single-visit office BP but daytime ambulatory instead of home BP.¹⁷ However, among subjects with elevated office BP, white-coat hypertension was common, particularly in the untreated group (42.9%). This is probably because this analysis is based on single-visit office BP, which is known to be reduced in subsequent visits. Moreover, treated subjects are more familiar with the office environment, which might have reduced their office BP. On the contrary, among subjects with low office BP, masked hypertension was 3-fold more common in treated than in untreated subjects. This difference may be attributed to the fact that the antihypertensive treatment is mainly adjusted according to office BP, and that in treated subjects office BP is usually taken close to the peak effect of the drug treatment (few hours after morning drug intake), whereas home BP is measured at the trough (morning) and the plateau effect of treatment (evening). Moreover, treated subjects are more familiar with the office setting, which might have reduced their office BP. However, the prevalence of masked hypertension is particularly alarming (41.4% of treated subjects with normalized office BP and 16% of all treated subjects) and highlights the need for out-of-office BP evaluation in all treated subjects.

In the IDACO database in 648 untreated subjects with isolated systolic hypertension on office measurement, 52% had white-coat hypertension defined by ambulatory BP monitoring.¹⁸ In the same database, the prevalence of masked hypertension among untreated subjects with normal office BP was 19.2% compared with 31.9% in treated subjects.¹⁹ In the absence of studies assessing home and ambulatory BP in the same subjects, it is difficult to conclude whether the prevalence of white-coat and masked hypertension differs when defined by ambulatory or home measurements. The Pressione Arteriose Monitorate E Loro Associazioni (PAMELA) outcome study that performed office, home, and 24-hour ambulatory BP measurements in a general population sample of 2051 subjects in Italy^{20,21} showed similar prevalence of masked hypertension detected by home or ambulatory monitoring and slightly higher prevalence of white-coat hypertension with ambulatory monitoring. However, in the PAMELA study, the potential of home BP monitoring has not been exhausted because only 2

home readings were obtained, which are known to give higher and more variable values than measurements during the next days²² and less predictive of stroke risk.²³ Cross-sectional studies reported similar proportions of white-coat and masked hypertension detected by home or ambulatory monitoring with reasonable diagnostic agreement between the 2 methods.^{24,25}

Cardiovascular Event Rate in Untreated Versus Treated Subjects

Treated subjects were at significantly higher cardiovascular risk than the untreated ones, after adjustment for several major risk factors, many of whom were more prevalent in the treated group. Interestingly, treated subjects with low office and home BP had 54% higher cardiovascular risk than untreated normotensives. This has previously been noted in outcome studies with ambulatory BP monitoring¹⁷ and suggests that treatment, per se, is a marker for undetectable residual confounding risk factors, which are not eliminated by treatment.

This study showed that in untreated subjects, white-coat hypertension defined by home BP measurement is associated with higher cardiovascular risk than normotension. This is probably related, at least in part, to the higher home BP levels compared with the normotensive subjects. Sensitivity analyses suggested that this finding was limited to men who are at higher cardiovascular risk than women. In fact, white-coat hypertension seemed to have similar risk to that of masked hypertension but lower than that of sustained hypertension (Table 2). During the long follow-up (median 8.3 years), several individuals with prehypertension might have developed sustained hypertension. It is clear from the Figure that it takes a long time for the event curves to clearly separate, which is supported by similar data with ambulatory BP monitoring.²⁶

On the contrary, in the treated group, the white-coat phenomenon did not seem to be related with increased cardiovascular risk, which might be because of effective treatment of these subjects on the basis of their elevated office BP²⁷ and to the higher risk in the reference group. On the contrary, treated subjects with masked hypertension were at significantly higher risk than normotensive subjects and subjects with white-coat hypertension, which might be attributed to inadequate treatment of these patients because of their low office BP.

The lack of the prognostic value of the office BP in treated patients is supported by previous reports. The Ohasama study suggested a weakness of office BP for prediction of stroke risk in treated patients in contrast to home BP.²⁸ Some of the participants originally with white-coat hypertension are expected to move to normotension group by antihypertensive medication during follow-up, which might have attenuated the difference in the risk between normotension and white-coat hypertension. In addition, a meta-analysis showed that the treatment-induced BP reduction is smaller for ambulatory than for office BP.²⁹ These findings explain, at least in part, the fact that a proportion of treated patients originally classified to the sustained hypertension group is assigned to masked hypertension when treatment is initiated. In a recent IDACO analysis, the prevalence of masked hypertension was higher in treated individuals compared with untreated ones (42.5% versus 29.3%, respectively, for patients with diabetes mellitus and 30.4% versus 18.8% for nondiabetic patients).¹⁹ These observations may

account for the high cardiovascular risk in masked hypertension comparable with that in sustained hypertension.

Previous reports from the IDACO database based on ambulatory BP monitoring also provided information on the prognosis of white-coat and masked hypertension in untreated versus treated subjects.^{17,18} These 2 international databases have similar numbers of participants and follow-up (Table S2) and provide a unique opportunity to address the question whether white-coat and masked hypertension have similar prognostic value when identified by ambulatory or home BP measurements, although this would ideally require a data set including these measurements in the same subjects.

In contrast to the current analysis, in the IDACO database, untreated and treated white-coat hypertension assessed by ambulatory monitoring was not associated with increased cardiovascular risk compared with normotension, whereas masked hypertension did carry increased cardiovascular risk (Table S2).¹⁷ Another IDACO analysis in elderly subjects with isolated systolic hypertension also showed white-coat hypertension not to be associated with increased cardiovascular risk in both untreated and treated subjects.¹⁸ However, there was a trend toward higher risk in untreated versus treated subjects with white-coat hypertension compared with normotension (Table S2). Moreover, in the latter analysis, the cardiovascular risk of white-coat hypertension versus normotension was higher in untreated men and subjects with diabetes mellitus.¹⁸ The SHEAF (Self-measurement of blood pressure at Home in the Elderly: Assessment and Follow-up) study in treated elderly subjects assessed with home BP measurements is in line with the present findings by showing treated patients with white-coat hypertension to have similar cardiovascular risk as patients with controlled hypertension and subjects with masked hypertension to be at high risk similar to patients with sustained hypertension.³⁰

The finding that untreated white-coat hypertension is associated with increased risk when identified by home BP monitoring, whereas this was not the case in previous analysis with ambulatory BP monitoring, is challenging. The view that home and ambulatory BP are interchangeable methods because they both provide multiple out-of-office measurements is rather simplistic. These methods have major differences because home BP is monitored for several days, weeks, or months, but only in the sitting posture at home, whereas ambulatory BP is monitored only for 24 hours but in different conditions, at work, at home, and during sleep. The present study suggests that home and ambulatory BP are not interchangeable but probably complementary methods. This view is supported by a recent analysis of the PAMELA general population study where among subjects with white-coat hypertension (elevated office and low home or ambulatory BP) those with low home and ambulatory BP had lower cardiovascular mortality than those with only one of them being low.³¹

Terminology for White-Coat and Masked Hypertension

The terms white-coat and masked hypertension were used in this article to present the disagreement between office and home BP measurements in both untreated and treated subjects. It is accepted, however, that these terms are appropriate

for untreated subjects only. In the recent European Society of Hypertension position article on ambulatory BP monitoring, the terms white-coat effect and masked uncontrolled hypertension are used for treated individuals.³² Franklin et al distinguished unnecessarily treated white-coat hypertension from treated normalized hypertension with white-coat effect; the latter referring to patients with sustained hypertension whose out-of-office, but not in-office, BP normalized on antihypertensive treatment.¹⁸

Limitations

These results should be interpreted by taking into account several limitations. The major limitation of this kind of outcome studies is the lack of information during follow-up on BP levels, treatment for hypertension, and other risk factors. Without repeated assessment during the years of follow-up, it is not known how many normotensive subjects developed hypertension and how many untreated subjects received treatment, which probably influenced the outcome and may have diluted the true differences attributed to the white-coat and masked hypertension phenomena. Second, office BP was assessed at a single visit, which probably influenced the accuracy of hypertension diagnosis and the prevalence of the white-coat and masked hypertension. Third, different home BP measurement numbers and schedules have been used in the studies included in the meta-analysis, which may have affected the findings. Finally, the treated group was significantly smaller than the untreated (22.5%) group, yet with much higher cardiovascular event risk that is largely attributed to higher frequency of established risk factors.

Perspectives

The present analysis suggests that the classification of individuals on the basis of their office and home BP levels has significant prognostic relevance, which seems to differ in untreated and treated subjects. Masked hypertension carries the same risk as sustained hypertension in both untreated and treated subjects, whereas white-coat hypertension is a risk factor in untreated but not in treated subjects.

These data should be taken into account in the management of hypertension in clinical practice. Home and ambulatory BP should not be considered as interchangeable methods for the detection of untreated white-coat hypertension. Because of the abovementioned limitations of the studies included in this meta-analysis, more data are required to confirm these findings, by providing a direct comparison of home with ambulatory BP monitoring and with repeated assessment of BP levels and treatment status during follow-up.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Most of the evidence on the prognostic relevance of white-coat and masked hypertension is based on ambulatory BP monitoring. This article based on a database including 6458 participants from 5 population studies provides evidence on the prognostic significance of these conditions detected by home BP measurements.
- The database allowed separate powered analyses of the prognostic relevance in untreated and treated subjects.

What Is Relevant?

- The prognostic relevance of white-coat and masked hypertension detected by home measurements differs in untreated and treated subjects.
- Masked hypertension is associated with increased cardiovascular risk in both untreated and treated subjects.

- In contrast, white-coat hypertension is a cardiovascular risk factor in untreated but not in treated subjects. This finding is in the same direction with published data with ambulatory BP monitoring, although the latter did not reach significant difference compared with normotension.

Summary

Masked hypertension detected by home BP measurements is associated with increased cardiovascular risk in both untreated and treated subjects. However, white-coat hypertension is a cardiovascular risk factor in untreated but not in treated subjects.

Home BP monitoring might not be interchangeable with ambulatory monitoring for the detection and prognosis of white-coat hypertension in untreated subjects.

HYPERTENSION

Data Supplement

This Data Supplement has been provided by the authors to give readers additional information about their work.

Supplement to:
Prognosis of White Coat and Masked Hypertension: The International Database of Home Blood Pressure in Relation to Cardiovascular Outcome (IDHOCO) Hypertension 2013.

Table S1. Hazard Ratios for Cardiovascular Events in Subjects with White-Coat, Masked and Sustained Hypertension versus Normotension Obtained after Excluding one Cohort at a Time

| Excluded cohort | Normotension | White-Coat Hypertension | | | Masked Hypertension | | | Sustained Hypertension | | |
|--------------------|-------------------------|-------------------------|-------------------------|----------|-------------------------|-------------------------|----------|-------------------------|-------------------------|----------|
| | Events/ Participants | Events/ Participants | Adjusted HR (95% CI) | <i>P</i> | Events/ Participants | Adjusted HR (95% CI) | <i>P</i> | Events/ Participants | Adjusted HR (95% CI) | <i>P</i> |
| Untreated subjects | | | | | | | | | | |
| Ohasama | 63/1650 | 28/394 | 1.43 (0.91-2.24) | 0.12 | 23/235 | 1.43 (0.87-2.36) | 0.16 | 90/718 | 2.01 (1.42-2.86) | <0.0001 |
| Finn-Home | 112/2190 | 48/454 | 1.64 (1.16-2.30) | 0.0048 | 40/270 | 1.74 (1.20-2.52) | 0.0038 | 83/489 | 2.41 (1.78-3.27) | <0.0001 |
| Tsurugaya | 150/2816 | 60/625 | 1.37 (1.01-1.85) | 0.043 | 46/353 | 1.40 (1.00-1.97) | 0.052 | 124/737 | 2.07 (1.60-2.68) | <0.0001 |
| Didima | 144/2587 | 58/642 | 1.31 (0.97-1.79) | 0.082 | 50/373 | 1.54 (1.10-2.15) | 0.011 | 130/844 | 2.10 (1.62-2.72) | <0.0001 |
| Montevideo | 147/2693 | 62/665 | 1.44 (1.07-1.94) | 0.018 | 53/385 | 1.60 (1.16-2.22) | 0.0044 | 137/908 | 2.10 (1.63-2.70) | <0.0001 |
| Treated subjects | | | | | | | | | | |
| Ohasama | 25/166 | 18/132 | 1.25 (0.67-2.32) | 0.48 | 26/135 | 1.28 (0.72-2.28) | 0.40 | 80/508 | 1.21 (0.76-1.94) | 0.42 |
| Finn-Home | 50/254 | 37/150 | 1.22 (0.80-1.87) | 0.36 | 56/171 | 1.80 (1.22-2.66) | 0.0029 | 81/407 | 1.19 (0.83-1.71) | 0.34 |
| Tsurugaya | 48/269 | 43/200 | 1.27 (0.84-1.91) | 0.26 | 54/176 | 1.84 (1.24-2.73) | 0.0026 | 119/471 | 1.60 (1.13-2.27) | 0.0079 |
| Didima | 49/307 | 39/219 | 1.12 (0.73-1.71) | 0.60 | 63/218 | 1.90 (1.30-2.79) | 0.0009 | 122/613 | 1.51 (1.07-2.13) | 0.019 |
| Montevideo | 56/316 | 43/219 | 1.13 (0.76-1.68) | 0.56 | 65/228 | 1.74 (1.21-2.51) | 0.0028 | 134/645 | 1.43 (1.03-1.97) | 0.031 |

Hazard ratios express the risk versus the corresponding normotensive subgroup (untreated or treated respectively) and were stratified for cohort and adjusted for age, gender, body mass index, serum cholesterol, smoking status, cardiovascular disease history and diabetes mellitus. CI, confidence intervals.

Table S2. Cardiovascular Risk Associated with Untreated and Treated White Coat, Masked and Sustained Hypertension Identified by Ambulatory or Home Blood Pressure Measurement Compared to Normotension (Adjusted Hazard Ratios⁺ with 95% Confidence Intervals in Parentheses)

| Database (method for BP measurements) | Treatment | n | Follow-up (years) | White coat hypertension | Masked hypertension | Sustained hypertension |
|--|-----------|------|-------------------|-------------------------|---------------------|------------------------|
| IDACO (daytime ambulatory) ¹⁷ | No | 5510 | 9.5 | 1.25 (0.86–1.82) | 1.58* (1.17–2.12) | 1.91* (1.48–2.45) |
| | Yes | 1520 | | 1.15 (0.76–1.75) | 1.69* (1.12–2.57) | 1.65* (1.19–2.30) |
| IDACO (daytime ambulatory) ¹⁸ | No | 6439 | 10.6 | 1.17 (0.87–1.57) | 1.67* (1.33–2.09) | 1.43* (1.14–1.79) |
| | Yes | 856 | | 1.09 (0.79–1.52) | 2.02* (1.40–2.90) | 1.98* (1.55–2.53) |
| IDHOCO present study (home) | No | 5007 | 8.3 | 1.42* (1.06–1.91) | 1.55* (1.12–2.14) | 2.13* (1.66–2.73) |
| | Yes | 1451 | | 1.16 (0.79–1.72) | 1.76* (1.23–2.53) | 1.40* (1.02–1.93) |

IDACO, International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome; IDHOCO, International Database of HOme blood pressure in relation to Cardiovascular Outcome; *, Statistically significant increase in risk; +, Adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, diabetes mellitus, history of cardiovascular disease, and antihypertensive drug treatment.